

WHAT IS CLAIMED IS:

1 1. A method for the improvement of lung function, comprising administering
2 to a mammalian subject diagnosed with a disease or condition benefiting from the
3 improvement of lung function an effective amount of a molecule capable of inhibiting a
4 biological activity mediated by a TGF β -R1 kinase receptor.

1 2. The method of claim 1 wherein said disease or condition benefiting from
2 the improvement of lung function is selected from the group consisting of emphysema,
3 chronic bronchitis, chronic obstructive pulmonary disease (COPD), pulmonary edema,
4 cystic fibrosis, occlusive lung disease, acute respiratory deficiency syndrome (ARDS),
5 asthma, radiation-induced injury of the lung, lung injuries resulting from infectious
6 causes, inhaled toxins, or circulating exogenous toxins, aging and genetic predisposition
7 to impaired lung function.

1 3. The method of claim 1 wherein said disease or condition benefiting from
2 the improvement of lung function involves acute lung injury.

1 4. The method of claim 1 wherein said disease or condition benefiting from
2 the improvement of lung function is unaccompanied by lung fibrosis.

1 5. The method of claim 1 wherein said disease or condition benefiting from
2 the improvement of lung function is at a stage when lung fibrosis is not a major
3 symptom.

1 6. The method of claim 1 wherein said molecule specifically binds to said
2 TGF β -R1 kinase receptor.

1 7. The method of claim 1 wherein said molecule additionally inhibits a
2 biological activity mediated by p38 kinase.

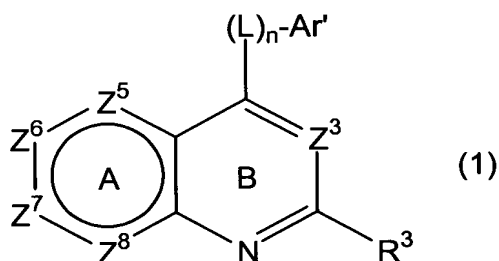
1 8. The method of claim 1 wherein said molecule preferentially inhibits a
2 biological activity mediated by TGF- β -RI kinase relative to a biological activity mediated
3 by p38 kinase.

1 9. The method of claim 1 wherein said compound is a non-peptide small
2 molecule.

1 10. The method of claim 9 wherein said compound is a small organic
2 molecule.

1 11. The method of claim 10 wherein said small organic molecule is other than
2 an imidazole derivative.

1 12. The method of claim 10 wherein said molecule is a compound of formula
2 (1)



3 or the pharmaceutically acceptable salts thereof

4 wherein R^3 is a noninterfering substituent;

5 each Z is CR^2 or N, wherein no more than two Z positions in ring A are N, and

6 wherein two adjacent Z positions in ring A cannot be N;

7 each R^2 is independently a noninterfering substituent;

8 L is a linker;

9 n is 0 or 1; and

10 Ar' is the residue of a cyclic aliphatic, cyclic heteroaliphatic, aromatic or

11 heteroaromatic moiety optionally substituted with 1-3 noninterfering substituents.

1 13. The method of claim 12 wherein said compound is a quinazoline
2 derivative.

1 14. The method of claim 13 wherein Z^3 is N; and Z^5 - Z^8 are CR^2 .

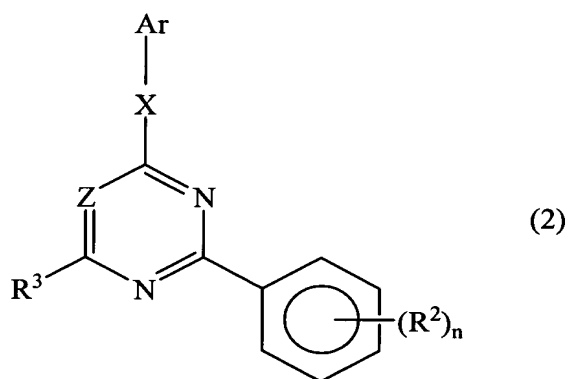
1 15. The method of claim 13 wherein Z^3 is N; and at least one of Z^5 - Z^8 is
2 nitrogen.

1 16. The method of claim 13 wherein R^3 is an optionally substituted phenyl
2 moiety.

1 17. The method of claim 16 wherein R^3 is selected from the group consisting
2 of 2-, 4-, 5-, 2,4- and 2,5-substituted phenyl moieties.

1 18. The method of claim 17 wherein at least one substituent of said phenyl
2 moiety is an alkyl(1-6C), or halo.

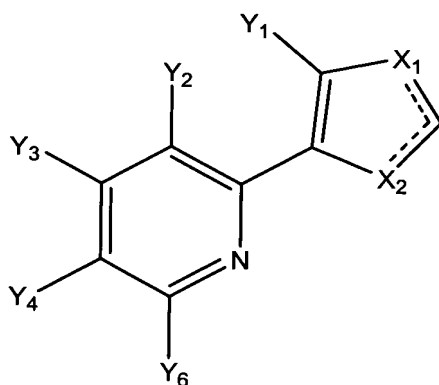
1 19. The method of claim 10 wherein said small organic molecule is a
2 compound of formula (2)



3 and the pharmaceutically acceptable salts and prodrug forms thereof; wherein
4 Ar represents an optionally substituted aromatic or optionally substituted
5 heteroaromatic moiety containing 5-12 ring members wherein said heteroaromatic moiety
6 contains one or more O, S, and/or N;
7 X is NR^1 , O, or S;
8 R^1 is H, alkyl (1-8C), alkenyl (2-8C), or alkynyl (2-8C);

9 Z represents N or CR⁴;
10 each of R³ and R⁴ is independently H, or a non-interfering substituent;
11 each R² is independently a non-interfering substituent; and
12 n is 0, 1, 2, 3, 4, or 5.

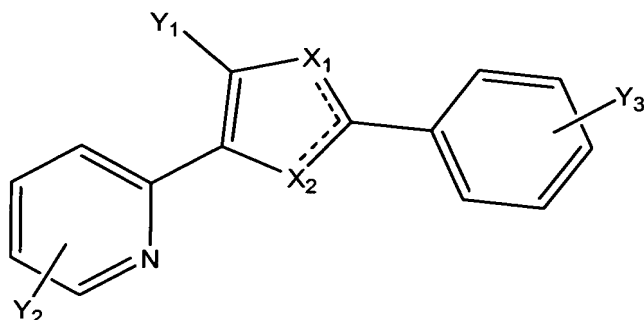
1 20. The method of claim 10 wherein said small organic molecule is a
2 compound of formula (3)



3 wherein Y₁ is phenyl or naphthyl optionally substituted with one or more
4 substituents selected from halo, alkoxy(1-6 C), alkylthio(1-6 C), alkyl(1-6 C), haloalkyl
5 (1-6C), -O-(CH₂)_m-Ph, -S-(CH₂)_m-Ph, cyano, phenyl, and CO₂R, wherein R is hydrogen
6 or alkyl(1-6 C), and m is 0-3; or phenyl fused with a 5- or 7-membered aromatic or non-
7 aromatic ring wherein said ring contains up to three heteroatoms, independently selected
8 from N, O, and
9 Y₂, Y₃, Y₄, and Y₅ independently represent hydrogen, alkyl(1-6C), alkoxy(1-6 C),
10 haloalkyl(1-6 C), halo, NH₂, NH-alkyl(1-6C), or NH(CH₂)_n-Ph wherein n is 0-3; or an
11 adjacent pair of Y₂, Y₃, Y₄, and Y₅ form a fused 6-membered aromatic ring optionally
12 containing up to 2 nitrogen atoms, said ring being optionally substituted by one or more
13 substituents independently selected from alkyl(1-6 C), alkoxy(a-6 C), haloalkyl(1-6 C),
14 halo, NH₂, NH-alkyl(1-6 C), or NH(CH₂)_n-Ph, wherein n is 0-3, and the remainder of Y₂,
15 Y₃, Y₄, and Y₅ represent hydrogen, alkyl(1-6 C), alkoxy(1-6C), haloalkyl(1-6 C), halo,
16 NH₂, NH-alkyl(1-6 C), or NH(CH₂)_n-Ph wherein n is 0-3; and
17 one of X₁ and X₂ is N and the other is NR₆, wherein R₆ is hydrogen or alkyl(1-6 C).

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1 21. The method of claim 10 wherein said small organic molecule is a
2 compound of formula (4)



3 wherein Y₁ is naphthyl, anthracenyl, or phenyl optionally substituted with one or more
4 substituents selected from the group consisting of halo, alkoxy(1-6 C), alkylthio(1-6 C),
5 alkyl(1-6 C), -O-(CH₂)-Ph, -S-(CH₂)_n-Ph, cyano, phenyl, and CO₂R, wherein R is
6 hydrogen or alkyl(1-6 C), and n is 0, 1, 2, or 3; or Y₁ represents phenyl fused with an
7 aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally
8 contains up to two heteroatoms, independently selected from N, O, and S;

9 Y₂ is H, NH(CH₂)_n-Ph or NH-alkyl(1-6 C), wherein n is 0, 1, 2, or 3;

10 Y₃ is CO₂H, CONH₂, CN, NO₂, alkylthio(1-6 C), -SO₂-alkyl(C1-6), alkoxy(C1-
11 6), SONH₂, CONHOH, NH₂, CHO, CH₂NH₂, or CO₂R, wherein R is hydrogen or
12 alkyl(1-6 C);

13 one of X₁ and X₂ is N or CR', and other is NR' or CHR' wherein R' is hydrogen, OH,
14 alkyl(C-16), or cycloalkyl(C3-7); or when one of X₁ and X₂ is N or CR' then the other
15 may be S or O.

1 22. A method for the treatment of a subject having impaired lung function
2 comprising administering to said subject an effective amount of a molecule capable of
3 inhibiting a biological activity mediated by a TGFβ-R1 kinase receptor.

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1 23. The method of claim 22 wherein said subject is human.

1 24. The method of claim 23 wherein said molecule specifically binds to said
2 TGFβ-R1 kinase receptor.

1 25. The method of claim 24 wherein said impaired lung function is associated
2 with a disease or condition selected from the group consisting of emphysema, chronic
3 bronchitis, chronic obstructive pulmonary disease (COPD), pulmonary edema, cystic
4 fibrosis, occlusive lung disease, acute respiratory deficiency syndrome (ARDS), asthma,
5 radiation-induced injury of the lung, lung injuries resulting from infectious causes,
6 inhaled toxins, or circulating exogenous toxins, aging and genetic predisposition to
7 impaired lung function.

1 26. The method of claim 25 wherein administration is in the form of a
2 pharmaceutical composition.

1 27. The method of claim 26 wherein said pharmaceutical composition is
2 suitable for oral administration.

1 28. The method of claim 26 wherein said pharmaceutical composition is
2 suitable for intravenous administration.

1 29. The method of claim 26 wherein said pharmaceutical composition is
2 suitable for aerosol administration.

1 30. The method of claim 26 wherein said pharmaceutical composition is
2 suitable for intrapulmonary administration.